APR 1 3 2001

K003412

Bayer Diagnostics

ASC:180 and ADVIA Centaur Rubella IgG assay

Summary of Safety and Effectiveness

As required by 21 CFR 807.92, the following 510(k) Summary is provided:

1. Submitter Information

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Date Summary Prepared:	January 19, 2001

2. Device Information

Proprietary Name: Common Name:	ADVIA Centaur Rubella IgG assay A chemiluminescence tests for the determination of IgM antibodies to the rubella virus
Classification Name: Class: CFR: Product Code:	Rubella Virus Serological Reagent Class II 21 CFR 866.3510 LSD

3. Predicate Device Information

Name:	AxSym Rubella IgG Antibody Assay IMx Rubella IgG Antibody Assay
Manufacturer:	Abbott Laboratories One Abbott Park Road Abbott Park, IL 60064
510(k) Number:	K954045 and K951541

4. Device Description

Rubella is a member of the togaviridae family. Primary infections are generally mild, with symptoms such as a mild rash, low-grade fever, and lymphadenopathy. In contrast, primary infections during pregnancy can pass transplacentally to the fetus and can lead to fetal death or

congenital rubella syndrome (CRS); the risk of fetal infection is greatest during the first trimester of pregnancy. Babies born with CRS typically exhibit low birth weight, deafness, eye disease, mental retardation, and cardiac abnormalities.

A primary infection induces an IgM and an IgG response. Within 4 to 6 months, IgM levels become undetectable or very low. IgG decreases to low levels, but lasts indefinitely and confers lifelong immunity. A secondary infection exhibits a rising IgG antibody without significant levels of IgM proportional to the quantity of anti-thyroid peroxidase antibody in the sample.

5. Statement of Intended Use

The ADVIA® Centaur™ Rubella IgG assay is an IgG antibody capture microparticle direct chemiluminometric immunoassay for the quantitative and qualitative detection of IgG antibodies to rubella virus in human serum or plasma (EDTA, heparin) as an aid in the assessment of immune status to rubella in individuals including women of childbearing age.

6. Summary of Technological Characteristics

The ADVIA Centaur Rubella G assay is a sandwich immunoassay using direct, chemiluminometric technology. The anti-human IgGFc monoclonal antibody is covalently coupled to paramagnetic particles in the Solid Phase. In the Lite Reagent, the rubella virus antigen is labeled with acridinium ester. The sample is incubated simultaneously with Solid Phase and Lite Reagent. Antibody-antigen complexes will form if rubella IgG is present in the sample.

A direct relationship exists between the amount of rubella IgG activity present in the patient sample and the amount of relative light units (RLUs) detected by the system. A result of positive or negative is determined according to the NCCLS suggested cutoff of 10 IU/mL established with the calibrators.

7. Performance Data

Non-clinical

Limitations

The use of the ADVIA Centaur Rubella G assay to diagnose recent infection by testing acute and convalescent sera samples has not been validated. The ADVIA Centaur Rubella G assay is limited to the detection of IgG antibodies to rubella virus in human serum or plasma.
Specimens taken early during the acute phase of infection may not contain detectable levels of IgG antibodies to rubella virus. The performance of the ADVIA Centaur Rubella G assay has not been established with cord blood, neonatal specimens, cadaver specimens, or body fluids other than serum or plasma, such as saliva, urine, amniotic, or pleural fluids. The performance of the assay has not been established for populations of immunocompromised or immunosuppressed patients.

Serum specimens that are...	Demonstrate ≤ 10% change in results up to . . .
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of triglycerides
icteric	60 mg/dL of conjugated bilirubin
	40 mg/dL of unconjugated bilirubin
proteinemic	3 g/dL of protein
hyper IgG	25 mg/mL of immunoglobulin G

Evaluation of Potential Interfering Disease States

To further evaluate the specificity of the ADVIA Centaur Rubella G assay, 100 specimens from individuals with the various disease states were tested. The rubella IgG status of the specimens was confirmed using an alternate method. The results are shown in the following table:

Disease State	Rubella IgG Status by Alternate Method	ADVIA Centaur Rubella G Assay Result < 10.0 (IU/mL)	≥ 10.0 (IU/mL)
Cytomegalovirus	Negative	3	0
	Positive	1*	6
Epstein-Barr virus	Negative	0	0
	Positive	0	10
Herpes simplex virus	Negative	3	0
	Positive	1*	6
Influenza vacinees	Negative	0	0
	Positive	0	10
Measles virus	Negative	0	0
	Positive	0	10
Parovirus B19	Negative	0	0
	Positive	0	10
Syphilis	Negative	1	0
	Positive	1*	8
Varicella zoster virus	Negative	1	0
	Positive	0	9
Multiple myeloma	Negative	2	0
	Positive	5**	3
Rheumatoid factor	Negative	0	0
	Positive	0	5
ANA	Negative	1	0
	Positive	1*	3

* Equivocal result on ADVIA Centaur Rubella G assay

** IgG concentration was greater than 25 mg/mL.

Precision

Reproducibility of the ADVIA Centaur Rubella G assay was determined as described in NCCLS protocol EP5-T2.[14] A sixteen member panel of serum and plasma was assayed two times in two separate daily runs, over a period of 20 days (n = 80). The following results were obtained using one reagent lot and a stored calibration curve:

Panel Member	Sample Type	N	Mean Concentration (IU/mL)	Within-run SD	Within-run % CV	Total** SD	Total** % CV
	Negative Control	80	0.0	0.02	NA*	0.05	NA
	Positive 1 Control	80	27.1	0.45	1.66	0.57	2.12
	Positive 2 Control	80	104.5	2.10	2.54	3.92	3.75
1	Serum	80	0.1	0.03	NA	0.15	NA
2	EDTA	80	0.1	0.03	NA	0.13	NA
3	Heparin	80	0.0	0.02	NA	0.10	NA
4	Sodium citrate	80	0.0	0.02	NA	0.11	NA
5	Serum	80	9.7	0.21	2.18	0.40	4.08
6	EDTA	80	9.4	0.18	1.86	0.31	3.32
7	Heparin	79	9.4	0.22	2.36	0.35	3.74
8	Sodium citrate	80	9.0	0.13	1.44	0.30	3.31
9	Serum	79	11.6	0.18	1.52	0.35	3.05
10	EDTA	80	11.3	0.23	2.08	0.37	3.27
11	Heparin	80	11.4	0.21	1.88	0.63	5.50
12	Sodium citrate	80	10.9	0.22	1.99	0.78	7.16
13	Serum	80	164.8	5.26	3.19	10.00	6.08
14	EDTA	80	180.4	5.04	2.80	11.90	6.62
15	Heparin	80	169.5	4.93	2.91	9.81	5.78
16	Sodium citrate	78	207.5	6.63	3.20	13.50	6.50

NA = Not Applicable.

** Includes within-run and run-to-run.

System reproducibility was determined by testing a 5 member panel with 3 reagent lots including 5 instruments and 3 sites over multiple days. The panel was assayed 3 times in each of 55 runs. The following results were obtained:

Panel Member	N	Mean Concentration (IU/mL)	Within-run SD	Within-run % CV	Total** SD	Total** % CV
Negative Control	168	0.33	0.04	NA*	0.06	NA
Positive 1 Control	165	19.90	0.31	1.57	1.28	6.41
Positive 2 Control	164	80.24	1.54	1.92	6.47	8.07
1	165	0.57	0.06	NA	0.14	NA
2	165	0.79	0.03	4.76	0.20	24.75
3	165	6.89	0.57	8.32	0.78	11.37
4	165	11.90	0.22	1.88	0.71	6.00
5	165	20.10	0.37	1.86	1.40	6.98

* NA = Not Applicable.

** Includes within-run and run-to-run.

Clinical Data

Expected Values

Among populations, the occurrence of IgG antibody to the rubella virus varies. The level of seropositivity ranges widely. Data was obtained on 990 samples from prenatal women and random individuals. Of these samples, 918 (92.7%) were positive, 35 (3.5%) were equivocal, and 37 (3.7%) were negative.

As with all in vitro diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

Population	N	Negative	Equivocal	Positive
Prenatal women	699	22 (3.1%)	23 (3.3%)	654 (93.6%)
Random individuals	291	15 (5.2%)	12 (4.1%)	264 (90.7%)

Sensitivity and Specificity

Relative Agreement
The presence of rubella IgG antibody in 1337 frozen and fresh specimens was evaluated at three U. S. sites using the ADVIA Centaur Rubella G assay and a commercially available rubella IgG EIA. Prenatal and random hospital and clinical specimens were obtained from the mid-Atlantic and Midwest regions of the United States as well as Canada and Germany. Of the 1337 specimens tested, 43 were equivocal by the ADVIA Centaur Rubella G assay. Discordant results were found on 9 specimens. Further evaluation was performed with the discordant samples using other commercially available tests for rubella IgG.

Relative Sensitivity

Using the alternative method, 1029/1337 tested positive for rubella IgG antibody. Of the specimens that tested positive, 23 were equivocal, 1000 were positive, and 6 were negative using the ADVIA Centaur Rubella G assay. The relative sensitivity was 99.4%.

Relative Specificity

Using the alternative method, 245/1337 tested negative for rubella IgG antibody. Of the specimens that tested negative, 5 were equivocal, 242 were negative, and 3 were positive using the ADVIA Centaur Rubella G assay. The relative specificity was 98.8%.
NOTE: Samples giving equivocal results were not included in the calculation of relative sensitivity, relative specificity, and relative agreement. Please be advised that 'relative' refers to the comparison of this assay's results to that of a similar assay. There was not an attempt to correlate the assay's results with disease presence or absence. No judgment can be made on the comparison assay's accuracy to predict disease.

Relative Sensitivity, Specificity, and Agreement before Resolution of Discordant Samples

Site	N	Relative Sensitivity (%)	Relative Specificity (%)	Relative Agreement (%)
1	645	100 (466/466)	99.4 (152/153)	99.8 (618/619)
2	350	98.9 (269/272)	100 (49/49)	99.1 (318/321)
3	342	98.9 (265/268)	95.4 (41/43)	98.4 (306/311)
Total	1337	99.4 (1000/1006)	98.8 (242/245)	99.3 (1242/1251)

		Predicate Rubella IgG Positive	Equivocal	Negative	Total
	Positive	1000	9	3	1012
ADVIA Centaur Rubella G	Equivocal	23	15	5	43
	Negative	6	34	242	282
	Total	1029	58	250	1337

Relative sensitivity = 99.4% (1000/1006), 95% CI (Confidence Interval) = 98.71– 99.78
Relative specificity = 98.8% (242/245), 95% CI = 96.46 – 99.75
Relative agreement = 99.3% (1242/1251), 95% CI = 98.64 – 99.67

Consensus Testing

Further analysis of the nine specimens with discordant results was performed using an additional commercially available EIA for rubella IgG. Of the three that were positive by ADVIA Centaur and negative by EIA, one was equivocal and two were positive by consensus. Of the six that were negative by ADVIA Centaur and positive by EIA, one was equivocal, one was positive, and four were negative by consensus.

CDC Panel

A serum panel obtained from the Centers for Disease Control (CDC) was tested using the ADVIA Centaur Rubella G assay. The testing was performed to provide additional information about the performance of the ADVIA Centaur Rubella G assay with a characterized serum panel. This is not an endorsement of the assay by the CDC. The panel consisted of 82 positive and 18 negative samples. The ADVIA Centaur Rubella G assay correctly identified all (100) panel members.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

APR 1 3 2001

Mr. William J. Pignato
Director of Regulatory Affairs
Bayer Corporation
63 North Street
Medfield, MA 02052-1688

Re: 510(k) Number: K003412
Trade/Device Name: ADVIA® Centaur™ Rubella IgG Assay
Regulation Number: 866.3510
Regulatory Class: II
Product Code: LFX
Dated: January 19, 2001
Received: February 7, 2001

Dear Mr. Pignato:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Good Manufacturing Practice for Medical Devices: General (GMP) regulation (21 CFR Part 820) and that, through periodic GMP inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K003412

Device Name: Bayer Diagnostics ADVIA Centaur Rubella IgG Assay

Indications for Use:

The ADVIA® Centaur™ Rubella IgG assay is an IgG antibody capture microparticle direct chemiluminometric immunoassay for the quantitative and qualitative detection of IgG antibodies to rubella virus in human serum or plasma (EDTA, heparin) as an aid in the assessment of immune status to rubella in individuals including women of childbearing age

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K003412

(PLEASE DO NOT WRITE BELOW THIS LINE--CONTINUE ON ANOTHER PAGE, IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-The-Counter Use _____

(Per 21 CFR 801.109)